

**A confidence interval
for the reaction index**

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In 1992, Brasch and Henseler (1) introduced the reaction index (RI) to assess the quality of patch-test preparations. This index has since been used by various researchers, but no one, to our knowledge, has understood that the RI is a statistical estimate from a given sample and therefore should have a measure of sampling variability with it. Although Brasch and Henseler gave the 'rule of thumb' that the RI should not be used with <100 non-negative test results, one would certainly prefer a mathematically derived confidence interval (CI) for the RI to assess statistical uncertainty. Recently, our group used a computer-intensive bootstrap experiment to achieve CIs for the RI (2).

Methods

The RI relates the number of allergic reactions to the number of non-negative reactions by the formula:

$$RI = \frac{a - q - i}{a + q + i} \quad (1)$$

where a is the number of allergic, q is the number of questionable, and i is the number of irritant reactions.

As can be seen from the formula, the RI is not a true proportion with a range of values from 0 to 1, thus precluding the use of the standard CI for a binomial proportion. In contrast, the RI can take values between -1 and 1.

However, writing $RI = a/(a + q + i) - (q + i)/(a + q + i)$ one can perceive the RI as the difference of two true proportions X and Y with $X = a/(a + q + i)$ binomially distributed with success probability $P = a/(a + q + i)$ and $n = (a + q + i)$ and $Y = (q + i)/(a + q + i)$ binomially distributed with $P' = (q + i)/(a + q + i) = 1 - a/(a + q + i) = 1 - P$ and $n = (a + q + i)$, respectively. We note that the two binomial distributions X and Y can be interpreted as arising from a two-component multinomial

distribution which gives their covariance (3, p. 7) as $Cov(X, Y) = -n \times P \times P' = -n \times P \times (1 - P)$. Using an elementary theorem from probability theory (4, p. 184) on the variance of the difference of random variables X, Y we find

$$\begin{aligned} \text{Var}(X - Y) &= \text{Var}(X) + \text{Var}(Y) \\ &\quad - 2\text{Cov}(X, Y) \\ &= nP(1 - P) \\ &\quad + nP'(1 - P') \\ &\quad - 2(-nP[1 - P]) \\ &= 4nP(1 - P) \end{aligned}$$

and thus the 95% CI for RI, which is

$$\begin{aligned} RI \pm 1.96 \frac{\sqrt{4nP(1 - P)}}{n} \\ = RI \pm 1.96 \times 2 \times \sqrt{\frac{P(1 - P)}{n}} \end{aligned}$$

where 1.96 equals the corresponding two-sided 5% quantile from the standard normal distribution. It is remarkable that the length of the confidence is exactly twice the length of the simple CI for a binomial proportion. However, this becomes intuitively clear by noting the range of values for the RI being twice the range for a proportion.

In terms of the original terms, this becomes

$$RI \pm 1.96 \times 2 \times \sqrt{\frac{a(q + i)}{(a + q + i)^3}}$$

For example, the 95% CI for the RI (estimated value: 0.651) for nickel sulfate 2.5% from the list of Brasch and Henseler (1) is (0.607, 0.694).

Discussion

To assess the sampling variability of the RI, we derived a CI. This is simple to calculate and we encourage researchers to use it in their future work. We finally point to the fact that the CI derived here is only valid asymptotically, that is, for large sample sizes. Although it has been reported for the simple CI for a binomial proportion

that $n \times P > 5$ would be enough for a valid CI also with moderate sample sizes (5, p. 26), other authors suggest being more cautious (6). In view of this and the close connection between the CI for a binomial proportion and that for the RI, we suggest that for a valid computation of the CI for the RI $n (= a + q + i)$ should be larger than 100, if $P (= a/(a + q + i))$ lies between 0.1 and 0.9. For values of P outside that interval, n should be somewhat larger. It is to be noted that the 'rule of thumb' given here is different from the original rule of Brasch and Henseler (1) although both rules recommend a total sample size of 100 non-negative reactions. While Brasch and Henseler gave a rule for the computation of the RI itself, our rule applies to the computation of a CI for the RI.

References

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